REMARKS

Applicants have amended claims 66 and 78 to recite "wherein said oligonucleotide comprises a 20 nucleobase portion having a gap segment, a first wing segment and second wing segment, said gap segment consisting of ten contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of five 2'-O-methoxyethyl nucleosides." New claim 89 recites "wherein said oligonucleotide comprises a 20 nucleobase portion having a gap segment, a first wing segment and second wing segment, said gap segment consisting of twelve contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of four 2'-O-methoxyethyl nucleosides." Support for these amendments can be found, for example, at pages 31-34, and particularly lines 9-25 of page 34. Applicants have added new claims 83-88 and 90-98. Support for these claims can be found for example, in the claims as originally filed, and the specification at page 65.

Applicants note that in the Examiner made the following argument regarding the previously pending claims:

> It is noted that the instant claims recite "wherein said oligonucleotide comprises a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each independently consisting of five 2'-O-methoxyethyl nucleosides." The term "consisting" does not limit the term "comprising" and therefore the oligonucleotides can comprise bases outside of the instantly recited sizes. *Office Action* at 7.

Applicants have amended the claims to clarify that the recited oligonucleotides in claims 66 and 78 comprise a 20 nucleobase portion having a gap segment and first and second wing segments, with the ten contiguous 2'-deoxy nucleosides of the gap segment flanked on both its 5' and 3' end with a wing segment consisting of five 2'-O-methoxyethyl nucleosides, while the recited oligonucleotide in claim 89 comprises a 20 nucleobase portion having a gap segment and first and second wing segments, the twelve contiguous 2'-deoxy nucleoside of the gap segment flanked on both its 5' and 3' end with a wing segment consisting of four 2'-O-methoxyethyl nucleosides. Thus, as amended, the pending claims recite oligonucleotides comprising 20 nucleobase portions having 5-10-5 or 4-12-4 gapmer configurations.

35 U.S.C. § 112, First Paragraph – New Matter

Claims 66, 70-75 and 78-82 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner argues that there is no support in the specification as filed for the recited limitation "said oligonucleotide comprises a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each of said second and third wing regions independently consisting of five 2'-O-methoxyethyl nucleosides." Applicants previously indicated that support for this amendment could be found on page 29 of the specification.

Applicants apologize for the confusion, and draw the Examiner's attention to pages 31-34 of the specification as filed, particularly lines 9-25 of page 34, for example, for support of the pending claim language. Applicants submit that the amendments in the pending claims are adequately described in the specification as filed, and therefore do not constitute new matter. Applicants therefore request withdrawal of the rejection of claims 66, 70-75 and 78-82 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description support.

35 U.S.C. § 103(a) – Obviousness

Claims 66, 70-75 and 78-82 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, in view of Nicklin *et al.* and Yu *et al.* The Examiner asserts that Nyce discloses respirable antisense oligonucleotides, but not "2'-O-methoxyethyl 2'-deoxy wings as instantly claimed." *Office Action* at 6. The Examiner asserts that Nicklin teaches 2' modifications including 2'-O'methoxyethyl modifications. The Examiner asserts that Yu teaches hybrid oligonucleotides which are "deoxyribonucleoside phosphorothioates flanked by two segments of contiguous 2'-O-methyl ribonucleoside phosphorothioates at the ends." *Id.*

Picking elements from each of the references, the Examiner asserts that "[i]t would have been obvious to incorporate 2' -O-methoxyethyl modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al. and it would have been obvious to incorporate a region of 2'-deoxy nucleosides flanked by two 2'-O-methoxyethyl wings into the antisense oligonucleotides taught by Nyce et al." *Id.* at 7. The Examiner states that one would have been motivated to modify the Nyce molecule because "Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity

for the RNA target." *Id.* Finally, the Examiner argues that "one would have been motivated to incorporate the 2'-O-methoxyethyl modifications into the instantly recited configuration of comprising a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each independently consisting of five 2'-O-methoxyethyl nucleosides because Yu et al. teach this gapmer configuration and teach that hybrid oligonucleotides comprising phosphorothioates and 2'-O-methyl nucleosides have greater activity and are more resistant to nuclease-mediated degradation than oligonucleotides with phosphorothioates only." *Id.* at 7-8 (emphasis added). The Examiner states that one would have a reasonable expectation of success that the chemical modifications taught by Nicklin and Yu were know to enhance the activity of antisense oligonucleotides. *Id.* Applicants respectfully traverse.

Applicants note that as amended, the pending claims 66 and 78 recite that an oligonucleotide comprising a 20 nucleobase portion with "said gap segment consisting of ten contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of five 2'-O-methoxyethyl nucleosides," while new claim 89 recites "said gap segment consisting of twelve contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of four 2'-O-methoxyethyl nucleosides." None of the cited references teach these limitations.

Contrary to the Examiner's assertion that "Yu et al. teach this gapmer configuration," Yu does not teach a 20 nucleobase portion with "said gap segment consisting of ten [or twelve] contiguous 2'-deoxy nucleosides flanked on its 5' and 3' ends by said first and second wing segments, each of said first and second wing segments independently consisting of five [or four] 2'-O-methoxyethyl nucleosides." Yu discloses 25 nucleobase oligonucleotides with central gap regions of thirteen, fifteen or seventeen 2'-deoxy nucleotides flanked by six, five or four 2'-O-methyl nucleobase wings, respectively. This is not a disclosure of a 20 nucleobase portion having a gap segment and first and second wing segments, with a 5-10-5 or 4-12-4 gapmer configuration as recited in the claims.

Applicants note that Yu teaches away from modifying the central gap regions which are 13, 15, and 17 nucleobases in length in oligonucleotides 2-4 of Yu to be 10 or 12 nucleobases in length as recited in the claims. Yu tested the anti-HIV activity of 8 different 25 base

oligonucleotides in a $CD4^+$ T-cell line infected with HIV. *Yu et al.* at 1687-1689. Yu reports that of the oligonucleotides tested, the oligonucleotides with the longer central deoxy gap, (15 and 17 bases long), were better than the ones which were shorter (13 bases), or did not have a central gap region (15 base deoxy portion with 10 base 2'-O-methyl wing). The authors summarize their results, noting that the oligonucleotide with the longest central gap (17 bases) was "the most active in this series and may be related to the presence of larger fragments (17 base-pair) which may retain substantial antisense activity even after the 3'- and 5'- ends have been digested." *Yu et al.* at 1689, first paragraph (emphasis added). Thus, Yu teaches away from modifying the central gap to be smaller, such as the ten and twelve nucleotide gap recited in the pending claims.

In addition, one must also modify Yu to replace the 2'-O-methyl nucleoside wings with 2'-O-methoxyethyl nucleoside wings as claimed. Because Yu does not teach 2'-O-methoxyethyl modifications, the Examiner turns to page 4 of the disclosure in Nicklin. Nicklin discloses more than 90 different 2'-modifications on page 4. The Examiner has given no reason why, in replacing the 2'-O-methyl disclosed in Yu, one would choose the recited 2'-O-methoxyethyl modification from all of the choices disclosed in Nicklin.

As Applicants noted in their previous response:

> Nicklin et al. teach a long series of 2'-modifications on page 4 as indicated by the Examiner. Applicants submit that there is no motivation to select the specific 2' -modification now claimed, nor to select the particular chimeric motif now claimed, let alone motivation to combine the two. This would required improper picking and choosing from two separate lists of parameters. This picking and choosing could only be achieved by the use of impermissible hindsight by the Examiner as there is no motivation by Nicklin et al. to select that single modification from the 2' -modifications listed in the specification and the particular chimeric configuration that is not specifically taught by Nicklin et al. The remaining references do not cure this deficiency. *Previous Response* at 4.

The Examiner found this argument persuasive, stating that "Applicant's arguments and/or amendments filed on 3/16/07, with respect to the rejections under 35 U.S.C. § 103(a) have been fully considered and are persuasive," and as a result, the Examiner withdrew the previous rejection. *Office Action* at 2 (emphasis added).

Applicants submit that the Examiner has not cured the deficiency of the previous rejection by the additional citation of Yu. While Yu discloses chimeric oligonucleotides, it does

not disclose the gapmer configuration recited in the claims and teaches away from modifications to the shorter gap portion recited in the claims. Nor does Yu provide any reason to choose from among the large generic class of more than 90 2'-modifications recited in Nickin to arrive at the single claimed species. Thus, the Examiner is no better off citing Yu than in the previous office action where Nicklin was cited.

The Examiner must still provide a reason for one of skill in the art to choose to modify the compound of Nyce as claimed, when doing do requires choosing a particular combination of modifications from the three cited references. This is in addition to the modification of Yu which does not disclose a 20 nucleobase portion having a gap segment and first and second wing segments in the configuration of a 5-10-5 or 4-12-4 gapmer, and teaches away from such a modification. Applicants submit that the present rejection is deficient for the same reason as the previous rejection, and Yu does not cure this deficiency. Applicants therefore request reconsideration and withdrawal of the rejection of claims 66, 70-75 and 78-82 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: _____

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(619) 235-8550

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